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(54) Title: IN SITU FORMATION OF POLYMERIC MATERIAL (57) Abstract The invention provides a pharmaceutically acceptable polymeric material formed in situ at a body surface and a process for the preparation of material. The polymeric material is formed by applying an anionic polymer and a cationic polymer to the surface in the presence of water.		

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In Situ Formation of Polymeric Material

This invention relates to polymeric material, for example, coatings, films and gels, especially pharmaceutically acceptable bioadhesive coatings,
5 films and gels and more specifically to improved methods for producing such coatings, films and gels.

Many polymers are known to be bioadhesive (i.e. able to adhere to biological surfaces, e.g. mucus, the
10 skin, mucosal surfaces, epithelium etc.) and the value of this property is well recognised. For example, bioadhesives may be used to adhere active agents to specific sites in the body for local drug administration, or to coat particular parts of the
15 body. However, when bioadhesives are applied to such surfaces in aqueous solution they may be easily washed off or mechanically removed, because the strength of adhesion of each individual bioadhesive molecule to the surface is not very high. This may lead to further problems if the bioadhesive materials contain active
20 agents intended for use at one particular site, but which are washed away to other sites.

Thus to improve the retention of bioadhesives at a surface they may be formed into films. Such films may be formed either by chemical crosslinking or by
25 physical interaction of the bioadhesive molecules as they come out of solution. However, all of the known methods of film formation have drawbacks with regard to their use at biological surfaces. For example, if bioadhesive films are formed before being applied to a
30 surface (e.g. by weaving polymer strands or by slow evaporation of aqueous solutions of the polymers) they

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will be awkward to apply to relatively inaccessible parts of the body (e.g. the back of the throat or the underside of the tongue); furthermore, for a number of biopolymers, much of the bioadhesive character of the films may be lost if they become too dry.

5

Alternatively, current methods for forming bioadhesive films directly on a surface require the use of volatile solvents, which quickly evaporate to leave a film, but which are not suitable for use on sensitive areas of a body (e.g. open wounds, mucosal surfaces, etc.).

10

A need exists for coatings, gels and/or films, especially bioadhesive coatings, gels and films, capable of being formed directly on surfaces which avoids the use of volatile solvents.

15

A further need exists for a formulation which is capable of forming a bioadhesive coating, film or gel in situ and which may be provided to the consumer in stable form in a single dosage form containing both components.

20

According to the invention there is provided a pharmaceutically acceptable polymeric material formed in situ at a body surface, wherein the material is formed by the reaction of:

25

- i) an anionic polymer or tripolyphosphate (component a); and
- ii) a cationic polymer (component b) in the presence of water.

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Further according to the invention there is provided a process for the preparation of a pharmaceutically acceptable polymeric material in situ at a body surface by applying

- 5 i) an anionic polymer or tripolyphosphate (component a) and;
ii) a cationic polymer (component b)
to the body surface wherein component a) is capable of reacting with component b) to form the polymeric
10 material.

Preferably the polymeric material is a bioadhesive coating, film or gel.

15 Preferably, the polymers are applied sequentially and the first applied polymer is a bioadhesive polymer.

Preferably component a) has one or more acid (proton donor) groups, for example -COOH and/or $\text{-SO}_3\text{H}$.

20

Preferably component b) has one or more basic (proton acceptor) groups, for example -NH_2 and/or NHCH_3 .

25 Component a) may be selected from any anionic polymers that are water-soluble or dispersible and that will form a coating, gel or film in the presence of component b). Preferred anionic polymers include water-soluble salts of hyaluronic acid, water-soluble salts of alginic acids (e.g. sodium alginate, potassium alginate), water-soluble or dispersible
30 salts of polyacrylic acids (e.g. sodium carbomers),

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xanthan gum, acacia, pectins, sterculia, carrageenan salts, polylactic acid and water-soluble cellulose derivatives (e.g. sodium carboxymethyl cellulose). Most preferred anionic polymers for use in the present invention are water soluble or dispersible carbomer salts, water-soluble salts of alginic acids and water-soluble salts of cellulose derivatives.

Mixtures of anionic polymers may be used, as long as they do not themselves crosslink to form films until component b) is added to them.

The concentration of component a) in the the bioadhesive coating, gels or films of the invention will depend upon a number of factors (e.g. the strength of the film, gel or coating to be produced, the solubility of the polymers, the required viscosity of the solution etc.). Generally the concentration will preferably be selected from the range 0.1 to 75% weight to volume (w/v), more preferably 0.5 to 25% w/v based on the composition as a whole.

Component b) may be selected from any cationic polymers that are water-soluble or dispersible and that will form a coating, film or gel in the presence of component a). Preferred cationic polymers include water-soluble chitosan salts (e.g. chitosan chloride, chitosan acetate), polylysine, chondroitin salts, diethylaminoethyl dextran, dermatan and keratan.

Mixtures of component b) may be used to

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form the bioadhesive films of the invention, as long as they do not interact to form a film themselves until they have been added component a).

5 The total amount of component b) in the bioadhesive coatings, films or gels of the invention will depend upon a number of factors including the amount of component a) used, the strength of film required, the effectiveness of component b), etc. Generally the concentration will be selected from 0.1 to 75% w/v,
10 more preferably 0.5 to 25% w/v of the composition as a whole.

 The preferred amount may be easily determined by simple experimentation, however the total weight ratio of component a) to component b) will generally be from
15 1:10 to 10:1, more preferably 1:2 to 2:1.

 The balance of the coating, film or gel may be water, any other pharmaceutically effective carriers, fillers and/or excipients.

20 Where component a) is a water-soluble alginate salt, component b) is preferably selected from water-soluble chitosan salts; diethylaminoethyl dextran and chondroitin sulphate; most preferably a water-soluble chitosan salt.

25 Where component a) is a water-soluble or dispersible carbomer salt, component b) is preferably selected from water-soluble chitosan salts; diethylaminoethyl dextran and chondroitin sulphate;
30 most preferably a water-soluble chitosan salt.

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Where component a) is sodium carboxymethyl cellulose, component b) is preferably a water-soluble chitosan salt.

5 The bioadhesive coatings, films or gels of the invention may optionally further comprise one or more pharmaceutically active agents, for either local or systematic delivery depending upon the site of application of the coating, film or gel.

10 Suitable active agents for use in such coatings, films or gels of the invention include analgesics, anti-inflammatory agents and antipyretics (e.g. acetaminophen, ibuprofen, naproxen, diclofenac, ketoprofen, choline salicylate, benzydamine, buprenorphine, hydrocortisone, betamethasone);
15 decongestants (e.g. pseudoephedrine, phenylephrine, oxymetazoline, xylometazoline); mineral salts (e.g. zinc gluconate, zinc acetate); cough suppressants (e.g. dextromethorphan, codeine, pholcodine);
20 expectorants (e.g. guaiphenesin, n-acetylcysteine, bromhexine); antiseptics (e.g. triclosan, chloroxylenol, cetylpyridinium chloride, benzalkonium chloride, amylmetacresol, hexylresorcinol, dichlorobenzyl alcohol, benzyl alcohol, dequalinium chloride, silver sulphadiazine); cardiovascular agents (e.g. glyceryl trinitrate); local anaesthetics (e.g.
25 lignocaine, benzocaine); cytoprotectants (e.g. carbenoxolone, sucralfate, bismuth subsalicylate); antiulcer agents (e.g. calcium carbonate, sodium bicarbonate, magnesium trisilicate, magaldrate, cimetidine, ranitidine, nizatidine, famotidine, omeprazole, pantoprazole); antihistamines (e.g.
30 loratidine, terfenadine, diphenhydramine,

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chlorphenhydramine, triprolidine, acrivastine);
antinausea agents (e.g. prochlorperazine,
sumatriptan), bowel regulatory agents (e.g.
diphenoxylate, loperamide, sennosides); antifungal
agents (e.g. clotrimazole); antibiotics (e.g.
5 fusafungine, tyrothricin) and antipsoriasis agents
(e.g. dithranol, calcipotriol).

Mixtures of the active agents may be included in
the coatings, films or gels of the invention where
10 appropriate.

The active agents may be contained in either of
components a) and b) before they are applied to the
body surface, but most preferably they are contained
in component a).
15

The concentrations of the active agents will
depend upon their standard dosages and whether they
are for local or systemic release etc. Generally the
suitable concentrations will be readily apparent to
one skilled in the art of formulation (normally a
20 concentration range of 0.001 to 10% w/v).

Components a) and b) may optionally contain
other suitable excipients depending upon the proposed
site of application. Examples of suitable excipients
25 include colours, pH adjusters, flavours, sweeteners,
preservatives, suspending agents or plasticisers. The
concentrations of such excipients will be readily
apparent to one skilled in the art of formulation
(although they will normally be used in a
concentration range of 0.001 to 10% w/v).
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In a first aspect of the present invention components a) and b) are present in aqueous solution.

5 For the purpose of this invention aqueous solutions of components a) or b) also include aqueous dispersions of said materials.

10 As hereinbefore described, the aqueous solution of component b) may be applied sequentially in any order or simultaneously with the aqueous solution of component a) but more preferably, the aqueous solution of component b) is applied after the aqueous solution of component a).

15 The amount of time between the application of the two aqueous solutions may vary depending upon the site of application. For example, where component a) applied first is a biopolymer for use in the throat, the two aqueous solutions should be applied within about 10 seconds of each other. In contrast, on a relatively dry, stable surface such as the arm the aqueous solution which is to be applied second may be
20 applied at any time within 5 minutes of the application of the solution applied initially.

25 It will be clear that the aqueous solution of component a) and the aqueous solution of component b) must be kept apart until they are combined as they are applied to the body surface.

30 The aqueous solutions of component a) and component b) may be applied to a surface by any suitable means, depending upon the nature and accessibility of the surface. For example, where the

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surface is a relatively large area that may be suitably positioned (e.g. the back of a hand, etc.) the solutions may be poured on. The solutions may also be applied by use of a dropper (e.g. an eye dropper);
5 or they may be painted on by use of a brush, although care must be taken not to dip the same brush into the component a) solution and then the component b) solution. Alternatively, the solutions may be dispersed from a double-chambered tube, or a double-barrelled syringe. Where the film is intended to be
10 formed in the oesophagus, the aqueous solutions may be applied by being drunk sequentially.

More preferably, the aqueous solutions of component a) and component b) may be sprayed onto the surface.
15

Any conventional spraying devices may be used for spraying the individual solutions, for example aerosol sprays, pump sprays or trigger sprays. Most preferably, the spray device will be a pump spray or a
20 trigger spray.

Optionally, the two aqueous solutions may be applied by different means, for example the aqueous solution containing component a) may be painted on and the aqueous solution containing component b) may be
25 sprayed on.

When an aqueous solution of component a) is applied to a surface and an aqueous solution of component b) is applied shortly thereafter (according to a preferred embodiment of this aspect of the
30 invention) only that portion of component a) which

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comes into contact with component b) will react to form a film. Thus a proportion of component a) (especially that in closest proximity to the surface) may not simply form a film but may be coated by the film formed above it. The film in this case is
5 effectively a coating which can thus encapsulate the unreacted component a) and help to prevent it being removed. Thus the film will coat a reservoir of substantially unreacted component a) in this case. This effect will be most pronounced when the two
10 aqueous solutions are sprayed onto the surface, because the droplets so formed will have the most suitable shape to maximise the encapsulation effect.

In a most preferred embodiment of this aspect of the invention there is provided a process for the
15 preparation of a pharmaceutically acceptable polymeric in situ at a body surface, the polymeric material coating a reservoir of substantially unreacted component a) and holding it in close proximity to the body surface, comprising the steps of applying an
20 aqueous solution of component a) onto the body surface and subsequently applying an aqueous solution of component b) onto the same surface. The method of application is preferably spraying.

Preferably the polymeric material is a bioadhesive
25 coating, film or gel.

In this embodiment, component a) is preferably a bioadhesive polymer, most preferably a water-soluble alginate salt and component b) is most preferably a water-soluble chitosan salt. Optionally, the aqueous
30 solution of component a) also comprises an active

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agent so that a reservoir containing some of the active ingredient may be formed in close proximity to the surface.

5 Further according to this first aspect of the present invention, there is provided the use of:
i) an anionic polymer or tripolyphosphate (component a); and
ii) a cationic polymer (component b)
(and optionally one or more active agents) for the
10 preparation of aqueous solutions for application to a body surface to form a pharmaceutically acceptable polymeric material thereon wherein component a) is capable of reacting with component b) to form the material.

15 Preferably the polymeric material is a bioadhesive coating, film or gel.

Preferably the coating includes a reservoir of substantially unreacted component a).

20 Optionally, the reservoir of unreacted component a) further comprises one or more active agents such as those exemplified above.

25 Still further according to this first aspect of the present invention there is provided a pharmaceutical pack comprising:

i) an aqueous solution of an anionic polymer or tripolyphosphate (component a); and
ii) an aqueous solution of a cationic polymer
30 (component b)

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wherein component a) is capable of reacting with component b) to form a pharmaceutically acceptable polymeric material in situ at a body surface and the pack is suitable for applying the two solutions to the body surface such that the polymeric material is formed at that surface.

Preferably the polymeric material is a bioadhesive coating, film or gel.

The pharmaceutical pack may comprise two discrete containers, one for each aqueous solution; but preferably the pack will comprise two containers which are joined together; or, most preferably, the pharmaceutical pack will comprise a single container having separate compartments for each aqueous solution.

Where the pharmaceutical pack is a single container it may have separate dispensing means for each solution. For example, there may be spray dispensing means fitted at each end of the container (or next to each other) to provide sequential spraying of the two aqueous solutions.

Alternatively, in a preferred embodiment, the pharmaceutical pack comprises a single dispensing means which is most preferably a spray-dispensing means. The dispensing means may be adjusted to either dispense both aqueous solutions simultaneously, or, more preferably, to dispense them sequentially, either by single or multiple activations of the dispensing means.

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Still further according to this first aspect of the invention, there is provided the use of a process as described above in therapy, and in particular for the treatment of diseases of the throat and mouth.

5

Still further according to this first aspect of the invention, there is provided the use of a process as described above for the preparation of a medicament for the treatment of disorders of the upper GI tract.

10

In a second aspect to the present invention, there is provided a non-aqueous formulation for forming a pharmaceutically acceptable polymeric material in situ at a body surface, the formulation including

i) an anionic polymer or tripolyphosphate
(component a);

15

ii) a cationic polymer (component b); and
iii) optionally a pharmaceutically acceptable inert filler or carrier

wherein component a) is capable of reacting with component b) to form the polymeric material in situ following application to or ingestion by a mammal.

20

Preferably the polymeric material is a bioadhesive coating, film or gel.

The formulation may be liquid or solid.

25

The pharmaceutically acceptable inert filler or carrier of the invention may include a glycol, for example propylene glycol, a medium chain triglyceride oil, for example, Miglyol (RTM) (Huls Chemicals), a glyceride, for example Transcutol (RTM) (Gattefosse)
and/or mannitol.

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The formulation of this aspect of the present invention may optionally include one or more active agents, for either local or systemic delivery depending upon the site of application of the film.
5 In the case of delivery to the mouth, for example, active agents may be included to provide a local effect such as an analgesic or antiseptic action and/or to provide a systemic effect (for example, an anti-histamine or an anti-nausea agent).

10

Suitable active agents for use in such films or gels of the invention are as described above.

Mixtures of active agents may be included in the formulation of the invention, where appropriate.
15

In addition, the formulations of the present invention may optionally contain other suitable excipients depending upon the proposed site and/or mode of application. Examples of suitable excipients are as described above with the inclusion of
20 granulating agents such as polyvinyl pyrrolidone, and/or magnesium stearate.

Preferably, the mammal is a human although it will be appreciated that the present invention can have
25 application in animals.

The present invention thus provides formulations which can be used for preparing pharmaceutically acceptable bioadhesive coatings, gels and films in situ. Unexpectedly, some of the films formed by this
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process also have improved properties such as strength and adhesion as a result of their targeted delivery.

5 In one embodiment of this second aspect to the present invention, the formulation is presented as a non-aqueous liquid formulation in which both component a) and component b) are dispersed or suspended.

Such a formulation may be taken orally by drinking or pouring, or by spraying.

10

Alternatively, in another embodiment of this second aspect to the present invention, the formulation may be in the form of a dry powder which contains components a) and b) (and optionally c)) as an intimate mixture. The powder is suitable for delivery to the mouth or throat via an inhaler. The powder granules, which are of a size of more than 10µm, provide a coating in the mouth or on the throat by absorbing water so that component a) and component b) may react to form a bioadhesive film.

15

20

Equally, in another embodiment of this second aspect the formulation may be presented in the form of a tablet or lozenge containing both components necessary to form a bioadhesive film. The tablet or lozenge may be bi-layered, in which case, component a) may be present in one half and component b) may be present in the other half. Alternatively, these components could be presented as an intimate mixture.

25

On ingestion of the tablet, salivation allows release and dissolution of component a) and component

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b) so that reaction occurs between them to form a bioadhesive film or a gelatinous mass.

Another embodiment of this second aspect to the present invention relates to a formulation which
5 employs a controlled-release capsule containing both component a) and component b) within a hard or soft capsule. The capsule is made from gelatin or a suitable equivalent and opens in the stomach to allow
10 reaction of components a) and b) to form a bioadhesive film or a gelatinous mass.

The novel formulations of the present invention are all one-component non-aqueous systems containing both component a) and component b). In situ, water
15 which is present at (or which may be provided at) the delivery site is absorbed by the formulation, thereby enabling component a) and component b) to react to form a bioadhesive film or a gel.

It will be appreciated by those skilled in the art that component a) and b) will not crosslink to form a
20 bioadhesive coating, film or gel unless in an aqueous environment. Significant advantages accrue from keeping components a) and b) in a non-aqueous (and therefore non-crosslinking) environment, particularly insofar as the two components may be stored together
25 without reacting therefore allowing simultaneous (and therefore quicker) application to a location in a single dosage form.

Components a) and b) may be applied to the surface
30 by any suitable means, depending upon the nature and accessibility of the surface and on the nature of

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formulation which is appropriate for delivery to the surface. For example, where the surface is a relatively large area that may be suitably positioned (e.g. an external surface such as the back of a hand, etc.) a liquid formulation may be poured on, or may be
5 applied by use of a dropper (e.g. an eye dropper), or may be painted on by use of a brush, or may be dispersed from a syringe. Where the film is intended to be formed in the oesophagus, the film could be produced by drinking a liquid formulation or by the
10 ingestion of a tablet or capsule formulation. When the film is to be formed on the back of the throat or in the nasal cavity, the dry powder formulation may be the most appropriate to ensure accurate delivery and film formation.

15 Any conventional spraying devices may be used for spraying the liquid formulation, for example aerosol sprays, pump sprays or trigger sprays.

Most preferably the spray device will be a pump
20 spray or a trigger spray.

Further according to this second aspect of the present invention. there is provided the use of the above formulation in therapy, and in particular for the treatment of diseases of the throat and mouth.
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Further according to this aspect of the present invention, there is also provided the use of the above formulation for the preparation of a medicament for the treatment of disorders of the upper GI tract.
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The bioadhesive coatings, films or gels according to the invention in this case may act as a barrier to prevent further damage/contamination to wounded areas of skin (e.g. wounds, or sites of eczema etc.), to soothe sore areas of the body (e.g. sore throats etc.); or as systemic drug delivery films (e.g. transdermal films on intact skin, sublingual delivery films on the underside of the tongue etc.). Such coatings, films or gels are particularly useful for local delivery of active agents, as they prevent the active agents from being washed away from the site of application, i.e. they minimise the effect of the active agent on the surrounding tissue (e.g. a topical anaesthetic in the throat).

The bioadhesive coatings, films or gels of the invention may be formed upon any surface of the mammalian body as required. Suitable surfaces include any region of the skin (for example to cover a wound or act as a drug delivery patch), the back of the throat or the oesophagus (e.g. to provide mechanical protection/soothing, or to deliver active agents locally or systematically); the underside of the tongue (as a sublingual dosage form the systemic delivery) or in the nasal cavity, vagina or rectum (as local drug delivery forms).

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The invention will now be illustrated by the following Examples.

5 **EXAMPLE 1**

A. Anionic Solution

	Sodium alginate (LFR 5/60, Pronova biopolymer)	2g
	Methyl paraben (preservative)	0.1g
10	Flavours, sweeteners, colours	q.s.
	Purified water to	100ml

B. Cationic Solution

	Chitosan chloride (Seacure CL 211, Pronova Biopolymer)	0.4g
15	Methyl paraben (preservative)	0.1g
	Flavours, sweeteners, colours	q.s.
	Purified water to	100ml

Solution A

- 20 1. Dissolve the methyl paraben, flavours,
 sweeteners and colours in the water.
 2. Create a vortex in the solution and disperse the
 chitosan hydrochloride. Stir until dissolved.

Solution B

- 25 1. Dissolve the methyl paraben, flavours,
 sweeteners and colours in the water.
 2. Create a vortex in the solution and disperse the
 sodium alginate. Stir until dissolved.

30 Between 0.2 and 1ml of each solution may be

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sprayed simultaneously onto the back of the throat to form a soothing protective film. This film is of particular benefit to those suffering from a sore throat.

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EXAMPLE 2

As Example 1 but the Anionic Solution (A) contains 5% w/v sodium alginate and the Cationic
10 Solution (B) contains 2% w/v chitosan hydrochloride

EXAMPLE 3

As Example 1 but the Anionic Solution (A) also
15 contains 0.66% w/v lignocaine hydrochloride.

A soothing protective film is formed when 0.5ml of Solution A immediately followed by 0.5ml of Solution B are sprayed onto the back of the throat.
20 The resulting film also delivers a dose of 3.3 mg of lignocaine hydrochloride providing a local anaesthetic effect.

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EXAMPLE 4A. Anionic Solution

5 As Example 1.

B. Cationic Solution

	Chitosan chloride (Seacure CL 211, Pronova biopolymer)	0.4g
10	Methyl paraben	0.1g
	Benzocaine	0.2g
	Amylmetacresol	0.16g
	Dichlorobenzyl alcohol	0.24g
	Flavours, sweeteners, colours	q.s.
15	Purified water to	100ml

Solution B

1. Dissolve the methyl paraben, flavours, sweeteners and colours in the water.
2. Add the benzocaine, amylmetacresol and
20 dichlorobenzyl alcohol. Stir until dispersed.
3. Create a vortex in the solution and disperse the chitosan chloride. Stir until dissolved.

25 Spray 0.5 ml of Solution B onto the throat immediately followed by 0.5 ml of Solution A. A soothing protective film having local antibacterial and local anaesthetic properties is formed at the back of the throat.

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EXAMPLE 5

As Example 1 but Solution A also comprises 3 g
5 dextromethorphan hydrobromide and 200 mg of menthol
BP.

When 0.5 ml of both Solutions A and B are
sprayed onto the back of the throat of a patient
suffering from a cough a demulcent film is produced
10 providing a local soothing action (due to the menthol)
and a systemic cough suppressant effect (due to the
dextromethorphan hydrobromide).

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EXAMPLE 6A. Anionic Solution

5	Carbomer (Carbopol 974P B. F. Goodrich)	0.25g
	Methyl paraben	0.1g
	Sodium hydroxide	to pH 7
	Flavours, sweeteners, colours	q.s.
	Purified water to	100ml

10 B. Cationic Solution

	Chitosan chloride (Seacure CL 211, Pronova Biopolymer)	2g
	Methyl paraben	0.1g
	Flavours, Sweeteners, colours	q.s.
15	Purified water to	100ml

Solution A

1. Dissolve the methyl paraben, flavours, sweeteners and colours in the water.
- 20 2. Create a vortex in the solution and disperse the carbomer. Stir until well dispersed.
3. Add sodium hydroxide (as a 20% aqueous solution) and stir slowly until homogenous.
4. Check pH is between 6.5 and 7.5 and adjust volume.

25

Solution B

1. Dissolve the methyl paraben, flavours, sweeteners and colours in the water.
2. Create a vortex in the solution and disperse the chitosan chloride. Stir until dissolved.

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When between 0.2 ml and 1 ml of both Solutions A and B are sprayed simultaneously onto the back of the throat of a sore throat sufferer a soothing protective film is formed.

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EXAMPLE 7

As Example 6 but Solution A also contains 0.16g amylmetacresol and 0.24g dichlorobenzyl alcohol.

10

EXAMPLE 8

As Example 6 but Solution A also contains 1.6g calcium carbonate and 2.6g sodium bicarbonate.

15

When a 5 ml spoonful of Solution A is swallowed, followed after 10 to 30 seconds by a 5 ml spoonful of Solution B, a protective film is formed in the oesophagus which has neutralisation capacity to protect against gastric reflux.

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EXAMPLE 9A. Anionic Solution

5	Sodium alginate (LFR 5/60, Pronova Biopolymer)	5g
	Methyl paraben	0.1g
	Flavours, sweeteners, colours	q.s.
	Purified water to	100ml

10 B. Cationic Solution

	Chitosan hydrochloride (Seacure CL 211, Pronova biopolymer)	1g
	Methyl paraben	0.1g
	Flavours, sweeteners, colours	q.s.
15	Purified water to	100ml

Solution A

1. Dissolve the methyl paraben, flavours, sweeteners and colours in the water.
- 20 2. Create a vortex in the solution and disperse the sodium alginate. Stir until dissolved.

Solution B

1. Dissolve the methyl paraben, flavours, sweeteners and colours in the water.
- 25 2. Create a vortex in the solution and disperse the chitosan chloride. Stir until dissolved.

When 0.2 to 1 ml of each solution are sprayed simultaneously onto the back of the throat a soothing protective film is formed.

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EXAMPLE 10

As Example 1 but Solution A also contains 216 mg
5 of buprenorphine hydrochloride.

When 0.1 ml of Solution A, followed immediately
by 0.1 ml of Solution B, are sprayed onto the
underside of the tongue a film is formed providing
systemic (sublingual) delivery of buprenorphine
10 hydrochloride.

EXAMPLE 11

As Example 1 but Solution A also contains 10 g
15 povidone iodine complex.

When 5 ml of Solution A, immediately followed by
5 ml of Solution B, are sprayed onto a skin wound a
protective/disinfecting film is formed.
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EXAMPLE 12A. Anionic Solution

	Amidated low methoxy Pectin	6g
5	Methyl paraben (preservative)	0.1g
	Flavours, sweeteners, colours	q.s.
	Purified water to	100ml

B. Cationic Solution

	Chitosan chloride	
10	(Seacure CL 211,	
	Pronova Biopolymer)	0.4g
	Methyl paraben (preservative)	0.1g
	Flavours, sweeteners, colours	q.s.
	Purified water to	100ml

15 Solution A

1. Dissolve the methyl paraben, flavours, sweeteners and colours in the water.
2. Create a vortex in the solution and disperse the amidated pectin. Stir until dissolved.

20

Solution B

1. Dissolve the methyl paraben, flavours, sweeteners and colours in the water.
2. Create a vortex in the solution and disperse the chitosan hydrochloride. Stir until dissolved.

25

Between 0.2 and 1ml of each solution may be sprayed simultaneously onto the back of the throat to form a soothing protective film. This film is of particular benefit to those suffering from a sore throat.

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EXAMPLE 13

As Example 12 but the Anionic Solution (A)
contains 10% pectin and the Cationic Solution (B)
contains 2% w/v chitosan hydrochloride.

5

EXAMPLE 14

As Example 12 but the Cationic Solution (B)
also contains 0.66% w/v lignocaine hydrochloride.

10

When 0.5ml of Solution B immediately followed by
0.5 ml of Solution A are sprayed onto the back of the
throat a soothing protective film is formed, which
also delivers a dose of 3.3 mg of lignocaine
hydrochloride providing a local anaesthetic effect.

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EXAMPLE 15A. Anionic Solution

5 As Example 12.

B. Cationic Solution

	Chitosan chloride	
	(Seacure CL 211,	
	Pronova biopolymer)	0.4g
10	Methyl paraben	0.1g
	Benzocaine	0.2g
	Amylmetacresol	0.16g
	Dichlorobenzyl alcohol	0.24g
	Flavours, sweeteners, colours	q.s.
15	Purified water to	100ml

Solution B

1. Dissolve the methyl paraben, flavours, sweeteners and colours in the water.
2. Add the benzocaine, amylmetacresol and
20 dichlorobenzyl alcohol. Stir until dispersed.
3. Create a vortex in the solution and disperse the chitosan chloride. Stir until dissolved.

25 Spray 0.5 ml of Solution B onto the throat immediately followed by 0.5 ml of Solution A. A soothing protective film having local antibacterial and local anaesthetic properties is formed at the back of the throat.

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- 30 -

EXAMPLE 16A. Anionic Solution

5	Low methoxy amidated pectin	6g
	Methyl paraben	0.1g
	Flavours, sweeteners, colours	q.s.
	Purified water to	100ml

B. Cationic Solution

10	Chitosan hydrochloride (Seacure CL 211, Pronova biopolymer)	1g
	Methyl paraben	0.1g
	Flavours, sweeteners, colours	q.s.
15	Purified water to	100ml

Solution A

1. Dissolve the methyl paraben, flavours, sweeteners and colours in the water.
2. Create a vortex in the solution and disperse the pectin. Stir until dissolved.

Solution B

1. Dissolve the methyl paraben, flavours, sweeteners and colours in the water.
2. Create a vortex in the solution and disperse the chitosan chloride. Stir until dissolved.

When 0.2 to 1 ml of each solution are sprayed simultaneously onto the back of the throat a soothing protective film is formed.

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Example 17

	Chitosan chloride (Seacure CL211, Pronova	
5	Biopolymer a.s.)	2g
	Sodium alginate (LFR5/60, Pronova Biopolymer	
	a.s.)	10g
	Flavours, sweeteners colours and	
	preservatives	q.s.
	Propylene glycol to	100g

10

The sodium alginate and chitosan chloride powders are dispersed in propylene glycol. The remaining ingredients are then added and mixed until dispersed to form a sprayable liquid formulation. The

15 formulation is filled into a suitable spray pack and between 0.2 and 1.0ml of the suspension is sprayed onto the back of the throat to provide a soothing protective film. This formulation is of particular benefit to sore throat sufferers.

20

Example 18

A formulation identical to that of Example 17 but including 0.66% lignocaine hydrochloride was prepared.

25 0.5ml of a solution of the formulation was sprayed onto the back of the throat to provide a soothing protective film. The film also delivered a dose of 3.3mg of lignocaine hydrochloride to provide a local anaesthetic effect.

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Example 19

5 A formulation identical to the formulation of
Example 18 but further including Benzocaine 0.2g,
Amylometacresol 0.16g, and Dichlorobenzyl alcohol
0.24g was prepared in the manner described in Example
17. 0.5ml of a solution of the formulation was sprayed
onto the back of the throat to provide a soothing
protective film which also delivered a dose of local
10 anaesthetic and an anti-bacterial agent. This
formulation provided a treatment for sore throats.

Example 20

15 The formulation of Example 20 is identical to the
formulation of Example 19, except that the propylene
glycol base was replaced by a medium chain
triglyceride oil (Miglyol, Huls Chemicals).

20

Example 21

The formulation of Example 21 is identical with the
formulation of Example 19, except that the propylene
glycol base is replaced by Transcutol (a glyceride-
25 based liquid from Gattefosse).

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Example 22

	Carbomer (Carbopol 974P, B.F.	
5	Goodrich)	0.25g
	Chitosan chloride (Seacure CL211,	
	Pronova Biopolymer a.s.)	2g
	Flavours, sweeteners colours and	
	preservatives	q.s.
	Medium chain triglyceride oil	
10	(Miglyol 812)	100g

The chitosan chloride powders are dispersed in propylene glycol. The remaining ingredients are then added and mixed until dispersed. The resulting dispersion is filled into a suitable spray pack.

15 Between 0.2 and 1.0ml of the suspension was sprayed onto the back of the throat to provide a soothing protective film. The film soothes sore throats. Further examples of non-aqueous liquid-bases which may be used alone or in combination are: Polyethylene glycol 200 to 400, evening primrose oil, neem tree

20 oil, vegetable oils such as arachis oil and tea tree oil.

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Example 23

5	Chitosan chloride (Seacure CL211, Pronova Biopolymer a.s.)	8mg
	Sodium alginate (LFR5/60, Pronova Biopolymer a.s.)	17mg
	Triclosan	25mg
	Lecithin	5mg
	Colloidal silicon dioxide	4.5mg
10	Medium chain triglyceride oil	500mg

The ingredients were mixed together and filled into a hard gelatin capsule shell using conventional liquid filling equipment for liquid filling hard gelatin capsules. The capsule was dispersed in 0.1M

15 hydrochloric acid at 37°C in order to simulate gastric conditions. The capsule ruptures and the contents gel to form a matrix due to the interaction of the polymers. The bulk of the gelled matrix remains intact for over 12 hours, slowly releasing the

20 triclosan by diffusion and erosion processes. On ingestion, the capsule provided slow release of the drug into the stomach to provide a continued concentration of triclosan in the stomach for several hours; this provided an effective treatment of

25 H.Pylori infections.

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Example 24

	Chitosan chloride (Seacure CL211,	
5	Pronova Biopolymer a.s.)	8mg
	Sodium alginate (LFR5/60,	
	Pronova Biopolymer a.s.)	17mg
	Pseudoephedrine Hydrochloride	120mg
	Lecithin	5mg
	Colloidal silicon dioxide	4.5mg
10	Medium chain triglyceride oil	500mg

The ingredients were mixed together and filled into a hard gelatin capsule shell using conventional liquid filling equipment for liquid filling hard gelatin capsules. The resulting capsule provides a slow release of water soluble drug over the period of 12 hours, with the advantage of reducing the required dosing frequency as compared with standard dosage forms such as tablets.

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Example 25

	Chitosan chloride (Seacure CL211,	10mg
5	Pronova Biopolymer a.s.)	
	Sodium alginate (LFR5/60, Pronova	
	Biopolymer a.s.)	30mg
	Triclosan	25mg
	Gelucire 53/60 (Gattefosse)	300mg

10 The Gelucire 53/60 was melted and the remaining
ingredients were added to the melt and dispersed. The
resulting mixture was filled into hard gelatin
capsules and allowed to set. On ingestion, the
capsule slowly released the contents from the waxy
matrix which had gelled at the surface due to the
15 interaction of the polymers.

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Example 26

5	Chitosan chloride (Seacure CL211, Pronova Biopolymer a.s.)	28.0%
	Sodium alginate (LFR5/60, Pronova Biopolymer a.s.)	71.0%
	Polyvinyl pyrrolidone (Povidone 30 (Kollidon 30 BASF))	1.0%
	Flavours, sweeteners and colour	q.s.

10

The Povidone was dissolved in ethanol to form a 2% solution suitable for granulating. The chitosan and the sodium alginate were mixed in dry form and a suitable amount of the granulating solution was added to form a wet mass. The wet mass was pushed through a 500µm screen and the screened wet mass was dried at 25°C overnight to remove the ethanol. The resulting dry granules were passed through a 150µm screen and fine particles were sieved off through a 53µm screen. The resulting granules were collected and filled into a size 2 capsule shell without compacting. The capsules were put into a Spinhaler (TM of Fisons) device and the device was primed to rupture the capsule so as to provide a dry powder for inhalation. The inhaled powder coated the inside of the mouth and throat and provided a soothing coating which protected against further mechanical irritation in the case of sore throats, sore mouths and ulcers.

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Example 27

5 The formulation of Example 27 is identical with
the formulation of Example 26, except that the
formulation of Example 27 also included benzocaine
hydrochloride. The benzocaine hydrochloride was added
to the granules in such an amount that each 40mg of
granules contained 10mg of benzocaine hydrochloride.
10 The formulation was coated inside the mouth in the
same manner as in Example 10 and provided local
anaesthetic pain relief in addition to the soothing
and protecting effects described above.

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Example 28

5 A bilayer tablet was formed using the following ingredients:

Layer one:

	Sodium alginate (LFR 5/60,	
	Pronova Biopolymer a.s.)	125mg
	Polyvinyl pyrrolidone	
10	(Povidone 30 (Kollidon 30 BASF))	25mg
	Mannitol	350mg
	Flavours and sweeteners	q.s.
	Magnesium stearate	15mg

Layer two:

15	Chitosan chloride (Seacure CL211,	
	Pronova Biopolymer a.s.)	50mg
	Polyvinyl pyrrolidone (Povidone	
	30 (Kollidon 30 BASF))	25mg
	Mannitol	425mg
20	Flavours and sweeteners	q.s.
	Magnesium stearate	15mg

Each layer was separately prepared in the same manner. For each layer, all the ingredients except the flavour and the magnesium stearate were mixed in a high-speed mixer granulator. The mixture was granulated by adding isopropanol (200mls per Kg) and the granulated mixture was subsequently dried at 50°C in a fluid bed dryer. The dried granules were sieved after which the flavour and magnesium stearate were added and mixed with the granules so as to give the final tablet mix for each layer. The two separate

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layers were then pressed into tablets on a bilayer
press. When the tablets were sucked, they slowly
released polymer from each side which then interacted
with each other to form a film on the surface of the
mouth and throat. The resulting film provided relief
5 for sufferers of dry mouth and sore throats.

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Example 29

The formulation of Example 29 is identical to the
5 formulation of Example 28, except that the formulation
included calcium carbonate (100mg) and magnesium
trisilicate (100mg) in each layer. On sucking the
bilayer tablets, the polymers interacted to form a
neutralising coating in the oesophagus which protected
against acid reflux.

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Example 30Layer one:

	Carbomer (Carbopol 974P, BF Goodrich)	80mg
5	Sodium bicarbonate	15mg
	Polyvinyl pyrrolidone (Providone	
	30 (Kollidon 30 BASF))	25mg
	Mannitol	350mg
	Flavours and sweeteners	q.s.
	Magnesium stearate	15mg

10

Layer two:

	Chitosan chloride (Seacure CL211,	
	pronova Biopolymer a.s.)	50mg
15	Polyvinyl pyrrolidone (Providone	
	30 (Kollidon 30 BASF)	25mg
	Mannitol	425mg
	Flavours and sweeteners	q.s.
	Magnesium stearate	15mg
	Lignocaine hydrochloride	3.3mg

20

The bilayer tablet was prepared in the same manner as for Example 28. When sucked, the bilayer tablet provided a local anaesthetic to the mouth and throat which relieved the pain of ulcers and sore throats. The polymers reacted to give a soothing protective film which additionally held the local anaesthetic in place so as to give a longer duration of action.

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Further active ingredients which are suitable for incorporation in a sustained release formulation such as those exemplified above include:

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Pseudoephedrine hydrochloride
Dextromethorphan hydrobromide
Diclofenac sodium
Ketoprofen
5 Theophylline hydrobromide
Sodium cromoglycate
Ketoconazole
Isosorbide dinitrate

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Claims

1. A pharmaceutically acceptable polymeric material formed in situ at a body surface, wherein the material is formed by the reaction of
 - i) an anionic polymer or tripolyphosphate (component a) and;
 - ii) a cationic polymer (component b) in the presence of water.
2. A process for the preparation of a pharmaceutically acceptable polymeric material in situ at a body surface by applying
 - i) an anionic polymer or tripolyphosphate (component a) and;
 - ii) a cationic polymer (component b) to the surface wherein component a) is capable of reacting with component b) to form the polymeric material in the presence of water.
3. The use of
 - i) an anionic polymer or tripolyphosphate (component a) and;
 - ii) a cationic polymer (component b) (and optionally one or more active agents) for the preparation of aqueous solutions for application to a body surface to form a pharmaceutically acceptable polymeric material thereon, wherein component a) is capable of reacting with component b) to form the material.
4. A pharmaceutical pack comprising an aqueous solution of

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- i) an anionic polymer or tripolyphosphate
(component a) and;
ii) a cationic polymer (component b)
wherein component a) is capable of reacting with
component b) to form a pharmaceutically acceptable
polymeric material in situ at a body surface and the
pack is suitable for applying the two solutions to the
body surface such that the polymeric material is
formed at that surface.
- 5
- 10 5. A non-aqueous formulation for forming a
pharmaceutically acceptable polymeric material in situ
at a body surface, the formulation including
i) an anionic polymer or tripolyphosphate
(component a);
ii) a cationic polymer (component b) and;
15 iii) optionally a pharmaceutically acceptable inert
filler or carrier
wherein component a) is capable of reacting with
component b) to form the pharmaceutically acceptable
polymeric material in situ at a body surface following
application to or ingestion by a mammal.
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6. A material, process, use or pack as claimed in
any preceding claim wherein the polymeric material is
a bioadhesive coating, film or gel.
- 25 7. A material, process, use or pack as claimed in
any one of claims 1 to 4 and 6 wherein components a)
and b) are present in aqueous solution.
8. A process as claimed in any preceding claim
wherein components a) and b) are applied sequentially
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and the first applied component, preferably component a), is bioadhesive.

- 5 9. A material, process, use, pack or formulation as claimed in any one of claims 1 to 8 wherein component a) has one or more acid (proton donor) groups including -COOH and/or -SO₃H and component b) has one or more basic (proton acceptor) groups including -NHCH₃ and/or -NH₂.
- 10 10. A material, process, use, pack or formulation as claimed in any preceding claim, wherein component a) is selected from the group comprising: water-soluble salts of hyaluronic acid, water-soluble salts of alginic acids, water-soluble or dispersible salts of polyacrylic acids, xanthan gum, acacia, 15 pectins, sterculia, carrageenan salts, polylactic acid and water-soluble cellulose derivatives.
- 20 11. A material, process, use, pack or formulation as claimed in any preceding claim wherein the concentration of component a) in the polymeric material is 0.1 to 75% weight per volume (w/v), more preferably 0.5 to 25% w/v.
- 25 12. A material, process, use, pack or formulation as claimed in any preceding claim wherein component b) is selected from the group comprising: water-soluble chitosan salts, polylysine, chondroitin salts, diethylaminoethyl dextran, dermatan and keratan.
- 30 13. A material, process, use, pack or formulation as claimed in any preceding claim wherein the concentration of component b) in the polymeric

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material is 0.1 to 75% weight per volume (w/v), more preferably 0.5 to 25% w/v.

14. A material, process, use, pack or formulation
5 as claimed in any preceding claim wherein the
polymeric material further comprises one or more
active agents selected from the group consisting of
acetaminophen, ibuprofen, naproxen, diclofenac,
ketoprofen, choline salicylate, benzydamine,
buprenorphine, hydrocortisone, betamethasone;
10 decongestants including pseudoephedrine,
phenylephrine, oxymetazoline, and xylometazoline;
mineral salts including zinc gluconate and zinc
acetate; cough suppressants including
dextromethorphan, codeine and pholcodine; expectorants
15 including guaiphenesin, n-acetylcysteine and
bromhexine; antiseptics including triclosan,
chloroxylenol, cetylpyridinium chloride, benzalkonium
chloride, amylmetacresol, hexylresorcinol,
dichlorobenzyl alcohol, benzyl alcohol, dequalinium
chloride and silver sulphadiazine; cardiovascular
20 agents including glyceryl trinitrate; local
anaesthetics including lignocaine and benzocaine;
cytoprotectants including carbenoxolone, sucralfate
and bismuth subsalicylate; antiulcer agents including
calcium carbonate, sodium bicarbonate, magnesium
trisilicate, magaldrate, cimetidine, ranitidine,
25 nizatidine, famotidine, omeprazole and pantoprazole;
antihistamines including loratidine, terfenadine,
diphenhydramine, chlorphenhydramine, triprolidine and
acrivastine; antinausea agents including
prochlorperazine and sumatriptan; bowel regulatory
30 agents including diphenoxylate, loperamide and
sennosides; antifungal agents including clotrimazole;

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antibiotics including fusafungine; tyrothricin and antipsoriasis agents including dithranol and calcipotriol and mixtures thereof.

5 15. A material, process, use, pack or formulation as claimed in any preceding claim, wherein the body surface is the surface of a human or animal body.

16. A formulation as claimed in any preceding claim in the form of a non-aqueous liquid containing both
10 component a) and component b).

17. A formulation as claimed in any one of claims 6 to 15 in the form of a dry powder which contains both component a) and component b) as an intimate
15 mixture.

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 98/02410

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K9/70 A61K9/00 A61K9/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>WO 92 09636 A (BAKER CUMMINS DERMATOLOG) 11 June 1992</p> <p>see page 9, line 1-15 see page 10, line 31 - page 11, line 26 see page 12, line 26-33 see page 28, line 15-25 see page 29, line 12 - page 30, line 27 see examples 3,4 see claims</p> <p style="text-align: center;">--- -/--</p>	<p>1-4, 6-10, 12-15</p>

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

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Date of the actual completion of the international search

2 December 1998

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14/12/1998

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 98/02410

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>US 4 913 743 A (BRODE GEORGE L ET AL) 3 April 1990 see column 1, line 12-16 see column 3, line 1-19 see column 3, line 49-65 see column 9, line 4-12 see column 11, line 33 - column 12, line 14 see column 13, line 33-48 see claims 1,3,5</p>	<p>1-7, 9-13,15</p>
X	<p>PATENT ABSTRACTS OF JAPAN vol. 006, no. 197 (C-128), 6 October 1982 & JP 57 106611 A (SANWA KAGAKU KENKYUSHO:KK), 2 July 1982 see abstract</p>	<p>1-3, 6-10,12, 14,15</p>
X	<p>CHEMICAL ABSTRACTS, vol. 122, no. 16, 17 April 1995 Columbus, Ohio, US; abstract no. 196719, ABLETSHAUSER, C. ET AL: "Self supporting polymer films crosslinked in situ by simultaneous spraying of component solutions. I. Characterization and drug diffusion" XP002086419 see abstract & FARM. VESTN. (LJUBLJANA) (1994), 45(4), 297-309 CODEN: FMVTAV;ISSN: 0014-8229,</p>	<p>1-3,6,9, 10,12,15</p>
X	<p>US 4 814 176 A (MAKINO YUJI ET AL) 21 March 1989 see column 1, line 6-10 see column 3, line 18-27 see column 4, line 14 - column 5, line 37 see column 5, line 56-63 see examples see claims</p>	<p>5,17</p>
X	<p>WO 94 06484 A (NOVASSO OY ;STRUSZCZYK HENRYK (PL); KIVEKAES OLLI (FI)) 31 March 1994 see page 6, line 19 - page 7, line 7 see page 7, line 26-28 see page 8, line 31 - page 9, line 2 see page 11, line 18-36 see examples 8-11 see claims 1,6,7</p>	<p>1-6, 9-13,15, 16</p>

-/--

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 98/02410

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>WO 96 03973 A (LIFEGROUP SPA ;DELLA VALLE FRANCESCO (IT); LORENZI SILVANA (IT); C) 15 February 1996 see page 5, line 2-25 see page 29, line 1 - page 31, line 8 see examples 12,19,21,22 see claims 1,7</p> <p>-----</p>	1-4,6-15

INTERNATIONAL SEARCH REPORT

International application No.

PCT/GB 98/02410

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
In view of the large number of compounds described by the expressions "anionic polymer" and "cationic polymer" in claims, the search has been restricted to the polymers cited in the examples and claims 10 and 12 for economic reasons.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Inter national Application No

PCT/GB 98/02410

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